CHAPTER 11

NEUROLOGICAL ASSESSMENT

INTRODUCTION

Neurological signs and symptoms, as distinguished from overt diagnosable neurological disease, have been consistently associated with industrial exposure to chlorophenols, phenoxy herbicides, and TCDD. Thus, the neurological system comprises a major examination focal point in all dioxin morbidity studies. This report carefully separates central and peripheral neurological status from "neurobehavioral" parameters, which are discussed in Chapter 12, Psychological Assessment.

Based on animal experiments, neurotoxicity can be attributed to the compounds 2,4-D and TCDD. For low to moderate doses, both central and peripheral acute effects occur but appear to be reversible.[1-3] The effects of 2,4-D are presumably due to disruption in the neuromuscular transport system of organic acid anions.[4] A variety of 2,4-D experiments in several animal species generally shows a wide range of neural pathology including electroencephalographic (EEG) desynchronization, demyelination, myotonia, loss of coordination, and uncontrolled motor activity. No substantive data support the isolated neurotoxicity of 2,4,5-T.

Numerous case reports following accidental human exposures or suicide attempts with 2,4-D have shown a remarkable neurologic parallel to the animal studies.[5-10] In particular, 2,4-D and TCDD have been implicated in a wide array of central neurological signs and symptoms, including headache, vomiting, dizziness, disorientation, sleep disturbance, stupor, memory loss, loss of coordination, and EEG abnormalities or alterations from a baseline tracing.[5-7,9,11-13] Peripheral abnormalities have included demyelination, acute degeneration of ganglion cells, temporary paralysis, anesthesia, hyperesthesia, paresthesia, neuralgic pain, numbness, tingling, muscle pain, muscle fasciculations, depressed or absent deep tendon reflexes, weakness, decreased nerve conduction velocities, "polyneuritis," and limb fatigue.[5-16] These peripheral signs and symptoms in industrial workers have received the generic diagnostic label "neurasthenia." Both the number and severity of symptoms tended to aggregate in individuals with chloracne as contrasted to those without chloracne.[11,16,17]

In general, there is consistency between the various case reports of neurasthenia and results from uncontrolled clinical studies. Of particular relevance is the consistency in findings from studies of both industrial manufacturing and industrial accidents. This literature provides the clear-cut conclusion that neurological impairment is caused directly by exposure to 2,4-D and TCDD. Not answered satisfactorily in the literature, however, are the issues of complete reversibilty of observed signs and symptoms and the long-term impact on health and quality of life.

Because of the conclusive evidence that two of three Agent Orange ingredients cause neurological "disease," it follows that significant exposure to Agent Orange could manifest neurologic signs, symptoms, or sequelae. In fact, over 10 percent of Vietnam veterans who enlisted in the VA Agent Orange Registry cited one or more symptoms of the neurasthenic complex.[18]

The VA Registry is a comprehensive listing, predominantly of veterans alleging health impairments due to Agent Orange exposure. The Registry does not purport to be a scientific effort upon which cause-and-effect relationships can be established. Nonetheless, some individuals believe that the symptom array in the VA Registry is so compatible with case reports and numerator-oriented clinical studies that the veterans must, in fact, have suffered adverse health effects from their Vietnam service and presumed exposure to Agent Orange. Others point to the intense media attention to "Agent Orange symptoms" during the formation of the Registry, and presume that the veterans' complaints are largely due to an "over-reporting" or compensation bias.

Clearly, only well-controlled, well-conducted epidemiologic studies of veterans known to have been exposed to Agent Orange can answer the question of cause and effect for illnesses, including the specific question of whether single or multiple neurologic signs and symptoms are also attributable to these exposures.

Baseline Summary Results

The 1982 AFHS neurological assessment consisted of questionnaire, physical examination, and electromyographic data obtained by examiners and technicians who were blinded to the group identity of each participant. The physical examination required an average of 30 minutes to complete. Those few individuals with positive RPR tests, a screening serological test for syphilis, and those with peripheral edema were deleted from the statistical analyses. Covariates of reported alcohol usage, exposure to insecticides and industrial chemicals, and glucose intolerance (diabetes) were analyzed. Results of the questionnaire disclosed no significant group differences in reported neurological diseases.

The physical examination did not reveal any statistically significant group differences in the function of all 12 cranial nerves, nor any effects due to the covariates of alcohol or diabetes. Peripheral nerve function was assessed by the quality of four reflexes (patellar, Achilles, biceps, and Babinski), muscle strength/bulk, and reaction to the stimuli of pin prick, light touch, and vibration. Other than a statistically significant increase ($p=0.03$) in Ranch Hand Babinski reflexes, significant group differences were not detected. The alcohol covariate demonstrated a marginal effect ($p=0.07$) on pin-prick reaction, while glucose intolerance showed a profound effect on the patellar and Achilles reflexes and reactions to light touch and vibration.

Nerve conduction velocities were obtained on the ulnar nerve, above and below the elbow, and the peroneal nerve by highly standardized methods. The results for each segmental measurement were nearly identical in the Ranch Hand and Comparison groups. Conduction velocity showed highly significant inverse relationships to both alcohol (measured in drink-years) and glucose intolerance in almost all of the anatomic measurements. No group associations or interactions were detected with the covariates of industrial and degreasing chemicals and insecticides.

No significant group differences were detected in four measures of central neurological function (tremor, finger-nose coordination, modified positive Romberg's sign, or abnormal gait). Alcohol usage was significantly associated with the presence of tremor, and glucose intolerance was highly correlated to abnormal balance and the presence of tremor.

Of a total of 84 exposure index analyses on all of the dependent variables, 3 were statistically significant but were either nonlinear or biologically implausible. In summary, the detailed neurological examination and assessment did not reveal statistically significant increases in abnormalities in the Ranch Hands, nor were consistent dose-response relationships noted for herbicide exposure. The classical neurological effects of alcohol ingestion and diabetes were repeatedly observed in the neurological evaluations.

Parameters of the 1985 Neurological Assessment

The 1985 AFHS neurological examination deleted the measurements of nerve conduction velocities but otherwise repeated the format of the Baseline examination. The questionnaire maintained a historical focus of neurasthenia via five questions for the 1982-1985 interval.

With this similarity in examination and questionnaire, the dependent variables of the analyses were almost identical to those of the Baseline study, however, the number of covariates was slightly increased. Diabetic status was trichotomized: Individuals reporting a history of diabetes (unverified) and individuals exhibiting glucose intolerance with postprandial glucose levels greater than or equal to 200 mg/dl were classified as diabetic, participants with glucose levels of at least 140 mg/dl but less than 200 mg/dl were classified as impaired, and participants with glucose levels less than 140 mg/dl were classified as normal. Race was included as a covariate, and lifetime alcohol use was updated on the basis of enhanced information from the 1985 questionnaire.

The analyses were based on 1,016 Ranch Hands and 1,293 Comparisons. Individuals confirmed to be positive for syphilis by fluorescent treponemal antibody (FTA) testing were excluded from all analyses. Individuals with peripheral pitting or nonpitting edema were excluded only for the analyses of pin prick, light touch, and vibration. Numeric differences in the following tables are due to missing dependent variables or covariate data. The exclusions and missing covariate data are summarized in Table 11-1. The unadjusted analyses used chi-square or Fisher's exact test for frequency table analyses. Adjusted analyses were not performed where only sparse numbers of abnormalities were found. Logistic regression models were used in all adjusted analyses. Parallel analyses using Original Comparisons can be found in Appendix I, Tables I-3 through I-13.

RESULTS AND DISCUSSION

General

Detailed neurological data were obtained on all participants by standard physical examination techniques. Four board-certified SCRF neurologists, all

TABLE 11-1.

Exclusions and Missing Data for Neurological Assessment by Group

Data Category	Group: Ranch Hand	Group: Comparison	Total
Lifetime Alcohol History (Drink-Years); Missing Data	39	40	79
Peripheral Edema (Exclusion Category for Pin Prick, Light Touch, and Ankle Vibration)	13	16	29
Diabetic Class (Missing Data)	0	4	4
Positive Syphilis Serology (RPR and FTA) Exclusion Category	0	1	1

blinded to the exposure status of the participants, conducted the examinations. Data were collected to assess three specific clinical areas: cranial nerve function, peripheral nerve function, and central nervous system (CNS) function. The analyses in this chapter are presented in the order of these functional areas.

The unadjusted statistical analyses presented in this chapter are straightforward group contrasts of dichotomous (normal/abnormal) dependent variables using Fisher's exact test. Logistic regression models for adjusted analyses used the covariates of age (born in or after 1942, born between 1923 and 1941, born in or before 1922), race (Black, nonblack), occupation (OCC) (officer, enlisted flyer, enlisted groundcrew), diabetic class (DIAB) (normal, less than 140 mg/dl glucose; impaired, at least 140 mg/dl but less than 200 mg/dl glucose; diabetic, greater than or equal to 200 mg/dl glucose or past diabetic history), lifetime alcohol use (DRKYR) (total drink-years: 0, greater than 0 to 50, greater than 50), and unprotected exposure to insecticides (INS) (recorded as yes/no, excluding herbicide exposure). The models are "best-fit" following a step-down strategy beginning with all two-way interactions among the six covariates. Only variables with a substantial number of abnormalities were analyzed. Several summary indices were constructed for functionally related variables with low counts of abnormalities. A summary index was created for the cranial nerve function by combining the 15 cranial nerve parameters into a single index, which was classified as normal if all parameters were normal. Another cranial nerve function was created in a similar fashion, excluding neck range of motion due to the much higher percentage of abnormalities found for this variable relative to the other parameters. The four coordination parameters of the central nervous system were similarly combined to form a summary index. These constructed indices are presented more for the purpose of inspection than for inference making. Since the corneal reflex (as one measure of the trigeminal nerve function) contained no abnormalities for either group, no table is presented with this variable.

The statistical power to detect a given relative risk in many of the subsequent analyses was somewhat limited. With the use of a two-sided α-level of 0.05 and power of 0.80, the sample sizes were sufficient to detect a 49 percent increase in the frequency of abnormal values for neck range of motion, a 69 percent increase for light touch but only a doubling for tremor, and an elevenfold increase for gag reflex. Power was generally poor in these analyses because of the extremely small number of abnormalities observed in both the Ranch Hand and Comparison groups.

Questionnaire Data

For the interval questionnaire, each participant was asked to update his health history for neurologic conditions occurring between 1982 and 1985. All affirmative histories were subjected to medical record verification, and appropriate ICD-9-CM coding. All verified neurological diseases were placed into six broad disease categories. These data are summarized in Table 11-2.

TABLE 11-2.

Unadjusted Analysis for Verified Neurological Disease by Group*--1982-1985

	Group Abnormalities					
	Ranch Hand		Comparison			
Disease Category	Number	Percent	Number	Percent	Total	p-Value**
Inflammatory Diseases	0	0.0	0	0.0	0	--
Hereditary and Degenerative Diseases	2	0.2	0	0.0	2	0.194
Peripheral Disorders	18	1.8	27	2.1	45	0.651
Disorders of the Eye	5	0.5	7	0.5	12	0.999
Disorders of the Ear	6	0.6	7	0.5	13	0.999
Other Disorders	8	0.8	3	0.2	11	0.069

*Based on 1,016 Ranch Hands and 1,293 Comparisons; some participants may be classified in more than one category.

**Fisher's exact test.

All of these analyses were based on very small numbers of abnormalities, but none of the six general disease categories showed statistically significant differences between groups, although the marginal significance of the Other Disorders category is of interest.

To determine whether lifetime differences in neurologic disease exist between the Ranch Hand and Comparison groups, verified followup data were combined with verified Baseline historical data. This tabulation is presented in Table 11-3.

TABLE 11-3.

Unadjusted Analysis for Verified Neurological Disease by Group*--Baseline and First Followup Studies Combined

	Group Abnormalities					
	Ranch Hands		Comparisons			
Disease Category	Number	Percent	Number	Percent	Total	p-Value**
Inflammatory Diseases	3	0.3	2	0.2	5	0.660
Hereditary and Degenerative Diseases	2	0.2	3	0.2	5	0.999
Peripheral Disorders	23	2.3	38	2.9	61	0.361
Disorders of the Eye	16	1.6	23	1.8	39	0.747
Disorders of the Ear	24	2.4	29	2.2	53	0.889
Other Disorders	15	1.5	14	1.1	29	0.453

*Based on 1,016 Ranch Hands and 1,293 Comparisons; some participants may be classified in more than one category.

**Fisher's exact test.

Like the followup data, the combined data revealed no statistically significant differences in any disease category. Also, there was no significant difference in patterns of disease for each group (p=0.721).

Physical Examination Data

Dependent Variable and Covariate Relationships: Cranial Nerve Function, Peripheral Nerve Status, and Central Nervous System Coordination

Responses from both groups were combined and analyzed with the six covariates. In addition, current drinking (yes/no) and lifetime history of unprotected exposure to industrial and degreasing chemicals (yes/no) were also evaluated. Indices constructed from dependent variables from the cranial nerve function and central nervous system coordination processes were also included. A summary tabulation of covariate associations is shown in Table 11-4. The 10 variables in this table include variables from the peripheral nerve status and CNS process as well as the cranial nerve function and constitute the subset of variables for which adjusted analyses were performed.

These results generally showed the profound association of classical risk factors for neurological deficits. Increases in the percentages of abnormalities for Achilles reflex, muscle status, neck range of motion, and the cranial nerve function index (which included neck range of motion) were associated with increases in age. Increasing percentages of abnormalities for pin prick and light touch were noted for increasing age from the young category (3.4% and 2.7% for pin prick and light touch, respectively) to the middle-aged category (8.1% and 4.7%, respectively), but a declining proportion of abnormalities was observed from the middle- to older-age categories (7.3% and 1.2%, respectively). No age effect was noted for gait, the CNS index, the cranial nerve index (neck range of motion excluded), and, surprisingly, for tremor.

Race was not a significant covariate for any dependent variable. A significant occupational effect was observed for the CNS summary index ($p=0.021$, with both enlisted categories having a higher frequency of abnormalities [5.7% and 4.1% for enlisted flyers and enlisted groundcrew, respectively] than the officer category [2.6%]) and for the neck range of motion variable ($p=0.010$, with increasing proportions of abnormalities from the enlisted groundcrew [4.6%] to officers [7.5%] to enlisted flyers[8.0%]).

Abnormalities in the Achilles tendon reflex were related to a graduated increase in drink-years of alcohol. For the variables of pin prick, light touch, muscle status, neck range of motion, and cranial nerve index (with neck range of motion included), the 0 drink-year category was related to a higher frequency of abnormalities than the greater than 0 to 50 drink-year category, which in turn was associated with a lower frequency of abnormalities than the greater than 50 drink-year category. For the current drinker (which was not used for modeling), the percentage of abnormalities for Achilles reflex and gait was significantly greater ($p=0.007$ and $p=0.001$ for Achilles reflex and gait, respectively) for current nondrinkers than for current drinkers. This relationship was reversed for the CNS summary index.

For both the Achilles tendon reflex and the response to pin prick, the frequencies of abnormalities significantly increased from the diabetic classes of normal to impaired to diabetic ($p<0.001$ for both variables). For the variables of light touch, muscle status, gait, and CNS summary index, the associations with diabetic status were mixed: The normal diabetic class had a higher proportion of abnormalities than the impaired stratum which, in turn, had a lower proportion of abnormalities than the overtly diabetic class. Unexpectedly, the proportion of tremor abnormalities was highest for the normal diabetic class and became successively lower in the impaired and diabetic strata (2.48%, 0.45%, and 0%, respectively).

A higher proportion of pin prick abnormalities was associated with a history of unprotected exposure to insecticides ($p=0.040$; 6.94% for exposed versus 4.8% for unexposed). The other dependent variables were not

TABLE 11-4.

Association Between Seven Neurological Variables and Three Summary Indices and the Covariates in the Combined Ranch Hand and Comparison Groups

Dependent Variable	Covariate						Exposure		
	Age	Race	Occupation	Total Drink-years	Current Drinking*	Diabetic Class	Insecticides	Industrial Chemicals*	Degreasing Chemicals*
Achilles Reflex	<0.001	NS	NS	0.022	0.007	<0.001	NS	0.050	NS
Pin Prick	<0.001	NS	NS	0.004	NS	<0.001	0.040	NS	NS
Light Touch	0.027	NS	NS	0.006	NS	0.026	NS**	NS	NS
Muscle Status	<0.001	NS	NS	0.001	NS**	<0.001	NS	0.025	NS**
Gait	NS	NS	NS	NS	0.001	0.033	NS	NS	NS
CNS Index	NS	NS	0.021	NS	0.012	0.016	NS	NS	NS
Tremor	NS	NS	NS	NS	NS	0.011	NS	NS	NS
Neck Range of Motion	<0.001	NS	0.010	0.014	NS	NS**	NS	0.039	NS
Cranial Nerve Function Index	<0.001	NS	NS**	0.032	NS	NS	NS	NS**	NS
Cranial Nerve Function Index (Neck Range of Motion Excluded)	NS	NS	NS	NS**	NS	NS	NS	NS	NS

NS: Not significant (p>0.10).

* Variable not used in adjusted analyses.

NS**: Borderline significant ($0.05 < p \leq 0.10$).

significantly affected by the insecticide covariate. For most dependent variables, both Ranch Hands and Comparisons exposed to degreasing or industrial chemicals exhibited a smaller percentage of abnormalities than participants without exposure. Because the biologic basis of these findings is not readily apparent, these two variables were not used as adjusting covariates.

Cranial Nerve Function

All 12 cranial nerves were assessed as unilateral or bilateral; these unadjusted data are presented in Table 11-5. All bilateral assessments (e.g., right visual field, left visual field) were combined for the analyses; an abnormality consisted of a right and/or a left abnormality.

The analysis of the 12 variables and two cranial nerve function summary indices did not reveal statistically significant group differences. Since no abnormalities are present for the variables of speech and tongue position in the Comparison group, the estimated relative risk for these variables was approximated by adding 0.5 to each cell. The low frequency of abnormal counts in all variables, except neck range of motion, contrasts with the 1982 Baseline findings, which found substantially more abnormalities. For example, ocular movement was recorded as abnormal in more than 30 percent of the participants at Baseline while only 0.7 percent of participants were found to be abnormal at followup.

Because of the few abnormalities for all variables except neck range of motion, two summary indices of cranial nerve function were constructed. One indicated whether or not a participant is abnormal for any of the 15 variables, while the other was a composite for all except neck range of motion. The analyses of these indices are reflected in Table 11-5, and showed no statistically significant group differences, although the index excluding neck range of motion is of borderline significance. Speech and tongue position relative to midline were also of borderline significance, although the analysis was affected by sparse numbers of abnormalities. The constructed indices are presented more for the purpose of inspection than for inference making.

Because of sparse numbers of abnormalities, adjusted analyses were performed only on the variable neck range of motion and the cranial nerve function summary indices, with and without neck range of motion data. The results of these analyses are given in Table 11-6.

None of the results were statistically significant, although the cranial nerve function index, without neck range of motion, was marginally significant ($p=0.061$) when participants with missing drink-years were included. In the primary adjusted analysis for this variable, drink-years was included in a significant covariate interaction. However, an alternative model was also examined that included participants with missing drink-years due to the disparity in group response for these participants (4 out of 39 Ranch Hands abnormal, 0 out of 40 Comparisons abnormal). The results of these adjusted analyses are nearly identical to the unadjusted analyses (see Table 11-5). A borderline significant result of a group (GRP)-by-age interaction ($p=0.0501$) for neck range of motion existed, and an additional analysis stratifying by age is provided in Table 11-7. This table presents the results of interaction analyses from variables assessing the peripheral nerve status and central nervous system coordination process as well.

TABLE 11-5.

Unadjusted Analyses for Cranial Nerve Function by Group

Variable	Cranial Nerve	Statistic	Ranch Hand Number	Ranch Hand Percent	Comparison Number	Comparison Percent	Est. Relative Risk (95% C.I.)	p-Value
Smell	I Olfactory	n	1,016		1,292		1.27 (0.53,3.07)	0.654
		Abnormal	10	1.0	10	0.8		
		Normal	1,006	99.0	1,282	99.2		
Visual Fields	II Optic	n	1,016		1,292		1.27 (0.41,3.96)	0.774
		Abnormal	6	0.6	6	0.5		
		Normal	1,010	99.4	1,286	99.5		
Light Reaction	III Oculomotor	n	1,015		1,289		1.13 (0.43,2.94)	0.811
		Abnormal	8	0.8	9	0.7		
		Normal	1,007	99.2	1,280	99.3		
Ocular Movements	III Oculomotor IV Trochlear VI Abducens	n	1,016		1,292		0.76 (0.28,2.10)	0.801
		Abnormal	6	0.6	10	0.8		
		Normal	1,010	99.4	1,282	99.2		
Facial Sensation	V Trigeminal	n	1,014		1,290		2.55 (0.47,13.95)	0.415
		Abnormal	4	0.4	2	0.2		
		Normal	1,010	99.6	1,288	99.8		
Jaw Clench	V Trigeminal	n	1,016		1,292		1.27 (0.18,9.05)	0.999
		Abnormal	2	0.2	2	0.2		
		Normal	1,014	99.8	1,290	99.8		
Smile	VII Facial	n	1,016		1,292		2.23 (0.67,7.41)	0.230
		Abnormal	7	0.7	4	0.3		
		Normal	1,009	99.3	1,288	99.7		
Palpebral Fissures	VII Facial	n	1,015		1,292		1.28 (0.45,3.65)	0.789
		Abnormal	7	0.7	7	0.5		
		Normal	1,008	99.3	1,285	99.5		
Balance	VIII Acoustic	n	1,015		1,292		2.55 (0.23,28.15)	0.586
		Abnormal	2	0.2	1	0.1		
		Normal	1,013	99.8	1,291	99.9		

TABLE 11-5. (continued)

Unadjusted Analyses for Cranial Nerve Function by Group

Variable	Cranial Nerve	Statistic	Group: Ranch Hand Number	Ranch Hand Percent	Comparison Number	Comparison Percent	Est. Relative Risk (95% C.I.)	p-Value
Gag Reflex	IX Glosso-pharyngeal	n	1,014		1,291			
		Abnormal	1	0.1	1	0.1	1.27 (0.08,20.38)	0.999
		Normal	1,013	99.9	1,290	99.9		
Speech	X Vagus	n	1,016		1,291			
		Abnormal	3	0.3	0	0.0	8.92 (0.46,172.89)[a]	0.085
		Normal	1,013	99.7	1,291	100.0		
Tongue Position Relative to Midline	X Vagus	n	1,015		1,292			
		Abnormal	3	0.3	0	0.0	8.94 (0.46,173.19)[a]	0.085
		Normal	1,012	99.7	1,292	100.0		
Palate and Uvula Movement	XI Spinal Accessory	n	1,014		1,291			
		Abnormal	2	0.2	1	0.1	2.55 (0.23,28.16)	0.586
		Normal	1,012	99.8	1,290	99.9		
Neck Range of Motion	XII Hypoglossal	n	1,016		1,292			
		Abnormal	61	6.0	84	6.5	0.92 (0.65,1.29)	0.666
		Normal	955	94.0	1,208	93.5		
Cranial Nerve Function Index		n	1,003		1,275			
		Abnormal	96	9.6	115	9.0	1.07 (0.80,1.42)	0.663
		Normal	907	90.4	1,160	91.0		
Cranial Nerve Function Index (Neck Range of Motion Excluded)		n	1,003		1,275			
		Abnormal	42	4.2	35	2.7	1.55 (0.98,2.44)	0.062
		Normal	961	95.8	1,240	97.3		

[a]Estimated relative risk and 95% confidence interval calculated after adding 0.5 to each cell.

TABLE 11-6.

Adjusted Analyses for Selected Variables of Cranial Nerve Function by Group

Variable	Statistic	Ranch Hand Number	Ranch Hand Percent	Comparison Number	Comparison Percent	Est. Relative Risk(95% C.I.)	p-Value	Covariate Remarks*
Neck Range of Motion	n	1,016		1,292		0.90 (0.63,1.27)	0.531	AGE(p<0.001)
	Abnormal	61	6.0	84	6.5			GRP*AGE
	Normal	955	94.0	1,208	93.5			(marginal:p=0.0501)
Cranial Nerve Function Index	n	1,003		1,275		1.07 (0.80,1.42)	0.666	AGE(p<0.001)
	Abnormal	96	9.6	115	9.0			
	Normal	907	90.4	1,160	91.0			
Cranial Nerve Function Index (Neck Range of Motion Excluded)	n	964		1,232		1.42 (0.88,2.30)	0.153	DIAB*INS(p=0.022)
	Abnormal	38	3.9	34	2.8			OCC*DRKYR(p=0.011)
	Normal	926	96.1	1,198	97.2			OCC*DIAB(p=0.015)
	Alternative Model—Includes Missing Drink-Year Participants[a,b]							
	n	1,003		1,271		1.56 (0.98,2.49)	0.061	DIAB*INS(p=0.017)
	Abnormal	42	4.2	34	2.7			OCC*DIAB(p=0.016)
	Normal	961	95.8	1,237	97.3			

*Abbreviations:

GRP: group
DIAB: diabetic class
INS: insecticide exposure
OCC: occupation
DRKYR: drink-years

[a]Lifetime alcohol consumption (total drink-years) not used as a covariate.

[b]79 missing drink-year participants: 4/39 Ranch Hands abnormal; 0/40 Comparisons abnormal.

TABLE 11-7.

Summary Table of Group-by-Covariate Interactions for Neurological Variables

Variable	Interaction	Stratification	Statistic	Ranch Hands Number	Ranch Hands Percent	Comparisons Number	Comparisons Percent	Adj. Relative Risk (95% C.I.)	p-Value
Neck Range of Motion	Group-by-Age	Born ≥ 1942	n	412		549			
			Abnormal	10	2.4	5	0.9	3.03 (1.02,9.00)	0.045
			Normal	402	97.6	544	99.1		
		Born 1923-1941	n	568		693			
			Abnormal	47	8.3	70	10.1	0.82 (0.55,1.21)	0.319
			Normal	521	91.7	623	89.9		
		Born ≤ 1922	n	36		50			
			Abnormal	4	11.1	9	18.0	(0.55 (0.16,1.97)	0.361
			Normal	32	88.9	41	82.0		
Pin Prick	Group-by-Diabetic Class	Abnormal	n	76		94			
			Abnormal	13	17.1	10	10.6	1.74 (0.71,4.24)	0.223
			Normal	63	82.9	84	89.4		
		Impaired	n	105		174			
			Abnormal	1	1.0	16	9.2	0.09 (0.01,0.69)	0.021
			Normal	104	99.0	158	90.8		
		Normal	n	822		1,005			
			Abnormal	45	5.5	53	5.3	1.02 (0.68,1.54)	0.920
			Normal	777	94.5	952	94.7		
Tremor	Group-by-Insecticides Exposure	Exposed to Insecticides	n	703		683			
			Abnormal	22	3.1	8	1.2	2.60 (1.15,5.90)	0.022
			Normal	681	96.9	675	98.8		
		Not Exposed to Insecticide	n	313		605			
			Abnormal	4	1.3	11	1.8	0.69 (0.22,2.19)	0.532
			Normal	309	98.7	594	98.2		

The stratified analysis for neck range of motion showed a higher proportion of younger Ranch Hands with neck range of motion abnormalities than younger Comparisons (p=0.045). Although not statistically significant, middle-aged and older Comparisons had higher proportions of abnormalities than did the Ranch Hands.

Peripheral Nerve Status

Peripheral nerve integrity was assessed by light pin prick, light touch (cotton sticks), visual inspection (and palpation, if indicated) of muscle mass, vibratory sensation as measured at the ankle with a tuning fork of 128 Hz, three deep tendon reflexes (patellar, Achilles, and biceps), and the Babinski reflex. The unadjusted analyses are given in Table 11-8. As noted previously, the analyses of pin prick, light touch, and vibratory sensation excluded the 29 participants with peripheral edema. These results showed that peripheral nerve function did not vary significantly by group.

Adjusted analyses were performed by logistic regression on four peripheral nerve variables. The other variables had relatively sparse numbers of abnormalities. The covariates were age, race, occupation, drink-years of alcohol, diabetic class, and exposure to insecticides. These statistics are displayed in Table 11-9.

For the variables light touch, muscle status, and the Achilles reflex, group differences were nonsignificant; the results were nearly identical to the unadjusted analyses. For the variable pin prick, however, a significant group-by-diabetic class interaction (p=0.003) was observed. This interaction was explored and the results are depicted in Table 11-7. As shown, the interaction suggests a difference, due to a lower proportion of abnormal pin-prick results in Ranch Hand impaired diabetics than in Comparisons (Adj. RR: 0.09,95% C.I.: [0.01,0.69], p=0.021), whereas both the abnormal and normal diabetic classes showed no significant group differences.

Central Nervous System Coordination

CNS coordination was evaluated clinically with four variables: hand tremor, rapid finger-to-nose coordination, one-foot standing balance (modified Romberg sign), and observation of gait for at least 10 steps. In addition, a constructed variable, the CNS summary index, was derived by summarizing abnormalities from all four CNS variables. The unadjusted analyses of these five variables are shown in Table 11-10.

These results revealed no statistically significant group differences for the four primary CNS variables, although the borderline significance of tremor, with a higher proportion of abnormalities in the Ranch Hands, is interesting. The statistical power to detect a given relative risk was poor because of the small percentages of abnormalities. The CNS summary index was statistically significant, with Ranch Hands manifesting a higher proportion of abnormalities; this result should be interpreted with caution, however, since this index was constructed after the data were examined. Three of the five variables with sufficient proportions of abnormalities were adjusted by six covariates, and these results are summarized in Table 11-11.

TABLE 11-8.

Unadjusted Analyses for Peripheral Nerve Function by Group

		Group					
		Ranch Hand		Comparison			
Variable	Statistic	Number	Percent	Number	Percent	Est. Relative Risk (95% C.I.)	p-Value
Pin Prick	n	1,003		1,276			
	Abnormal	59	5.9	80	6.3	0.93 (0.66,1.32)	0.725
	Normal	944	94.1	1,196	93.7		
Light Touch	n	1,003		1,276			
	Abnormal	38	3.8	47	3.7	1.03 (0.67,1.59)	0.912
	Normal	965	96.2	1,229	96.3		
Muscle Status	n	1,016		1,292			
	Abnormal	26	2.6	33	2.6	1.00 (0.60,1.69)	0.999
	Normal	990	97.4	1,259	97.4		
Vibratory Sensation	n	1,003		1,276			
	Abnormal	11	1.1	10	0.8	1.40 (0.59,3.32)	0.510
	Normal	992	98.9	1,266	99.2		
Patellar Reflex	n	1,016		1,290			
	Abnormal	11	1.1	16	1.2	0.87 (0.40,1.89)	0.846
	Normal	1,005	98.9	1,274	98.8		
Achilles Reflex	n	1,009		1,284			
	Abnormal	58	5.7	75	5.8	0.98 (0.69,1.40)	0.999
	Normal	951	94.3	1,209	94.2		
Biceps Reflex	n	1,016		1,292			
	Abnormal	9	0.9	10	0.8	1.15 (0.46,2.83)	0.819
	Normal	1,007	99.1	1,282	99.2		
Babinski Reflex	n	1,011		1,287			
	Abnormal	4	0.4	5	0.4	1.02 (0.27,3.80)	0.999
	Normal	1,007	99.6	1,282	99.6		

TABLE 11-9.

Adjusted Analyses for Selected Variables of
Peripheral Nerve Function by Group

		Group						
		Ranch Hand		Comparison				
Variable	Statistic	Number	Percent	Number	Percent	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Pin Prick	n	1,003		1,273		****	****	GRP*DIAB(p=0.003)
	Abnormal	59	5.9	79	6.2			AGE(p<0.001)
	Normal	944	94.1	1,194	93.8			
Light Touch	n	964		1,236		1.02 (0.65,1.60)	0.921	OCC*RACE(p=0.013)
	Abnormal	37	3.8	46	3.7			AGE(p=0.043)
	Normal	927	96.2	1,190	96.3			DRKYR(p=0.031)
Muscle Status	n	977		1,248		1.00 (0.57,1.75)	0.999	DRKYR*AGE(p=0.009)
	Abnormal	25	2.6	31	2.5			DIAB*INS(p=0.039)
	Normal	952	97.4	1,217	97.5			
Achilles Reflex	n	971		1,240		1.00 (0.69,1.45)	0.999	DRKYR*OCC(p=0.016)
	Abnormal	56	5.8	71	5.7			AGE(p<0.001)
	Normal	915	94.2	1,169	94.3			DIAB(p<0.001)

****Group-by-covariate interaction—adjusted relative risk, confidence interval, and p-value are not presented.

TABLE 11-10.

Unadjusted Analyses for CNS Coordination Variables by Group

Variable	Statistic	Group: Ranch Hand Number	Group: Ranch Hand Percent	Group: Comparison Number	Group: Comparison Percent	Est. Relative Risk (95% C.I.)	p-Value
Tremor	n	1,016		1,292			
	Abnormal	26	2.6	19	1.5	1.76 (0.97,3.20)	0.069
	Normal	990	97.4	1,273	98.5		
Coordination	n	1,015		1,292			
	Abnormal	9	0.9	7	0.5	1.64 (0.61,4.43)	0.327
	Normal	1,006	99.1	1,285	99.5		
Romberg Sign	n	1,015		1,292			
	Abnormal	2	0.2	1	0.1	2.55 (0.23,28.15)	0.586
	Normal	1,013	99.8	1,291	99.9		
Gait	n	1,016		1,290			
	Abnormal	20	2.0	16	1.2	1.60 (0.82,3.10)	0.178
	Normal	996	98.0	1,274	98.8		
CNS Summary Index	n	1,015		1,290			
	Abnormal	48	4.7	39	3.0	1.59 (1.04,2.45)	0.036
	Normal	967	95.3	1,251	97.0		

TABLE 11-11.

Adjusted Analyses for Selected Variables of CNS Coordination by Group

		Group						
		Ranch Hand		Comparison				
Variable	Statistic	Number	Percent	Number	Percent	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks*
Tremor	n	1,016		1,288				GRP*INS
	Abnormal	26	2.6	19	1.5	1.70 (0.93,3.09)	0.080	(marginal:p=0.055)
	Normal	990	97.4	1,269	98.5			DIAB(p=0.001)
Gait	n	977		1,246				DIAB(p=0.030)
	Abnormal	20	2.0	15	1.2	1.74 (0.88,3.47)	0.110	DRKYR*INS(p=0.047)
	Normal	957	98.0	1,231	98.8			
CNS	n	1,015		1,286				
Summary	Abnormal	48	4.7	38	3.0	1.57 (1.01,2.43)	0.042	DIAB(p=0.003)
Index	Normal	967	95.3	1,248	97.0			OCC(p=0.018)

These statistics were quite similar to the unadjusted tests, and showed borderline significance for tremor, nonsignificance for gait, and significance for the CNS summary index. The unexpected inverse relationship of tremor abnormalities to diabetic classification is again noted. The borderline group-by-insecticide interaction was investigated, and the results are given in Table 11-7. As shown, the relative risk for Ranch Hands exposed to insecticides was statistically significant (RR: 2.60, 95% C.I.: [1.15,2.90], p=0.022), whereas the relative risk for unexposed Ranch Hands was nonsignificant. This finding may have both an operational and biologic foundation, because records indicate that some Ranch Hands were exposed to the insecticide Malathion®, a cholinesterase inhibitor, during insecticide missions for malaria prevention. Comparisons, by definition, did not fly these missions.

EXPOSURE INDEX ANALYSES

Exposure index analyses were conducted within each occupation cohort of the Ranch Hand group to search for dose-response relationships (see Chapter 8 for details on the exposure index). All 27 variables and three summary indices were explored (unadjusted for any covariates) as with the unadjusted tests for group differences discussed previously in this chapter. These variables were investigated using Pearson's chi-square test and Fisher's exact test. Adjusted analyses were performed by logistic regression for the 10 variables (7 neurological parameters and 3 summary indices) for which adjusted analyses of group differences were previously examined. These analyses were accomplished, adjusted for age, diabetic class, insecticide exposure, and drink-years (all discretized), and any significant pairwise interactions between the exposure index and these covariates. Race was not included in adjusted analyses because of the absence of any race effect in the previous group difference analyses. Overall significance in the proportion of abnormalities among the exposure index levels of low, medium, and high was determined, as well as contrasts in the proportion of abnormalities between the medium and low exposure levels, and between the high and low exposure levels. Exclusions were made as described previously.

Results of the adjusted analysis are presented in Table 11-12, and results for unadjusted analyses appear in Table I-1 of Appendix I. Results from further study of exposure index-by-covariate interactions are given in Table I-2 of Appendix I.

Unadjusted analyses revealed borderline significant differences among exposure index levels for pin prick in enlisted groundcrew (p=0.052) and Achilles reflex in enlisted flyers (p=0.059). The data did not support an increase in the proportion of abnormalities with increasing exposure levels, however.

Adjusted analyses yielded similar conclusions, in that significant or borderline significant results did not support an increase in the proportion of abnormalities with increasing exposure, and that very few significant results were observed. The pattern of abnormalities with the 10 variables was studied, and in no occupational strata was an increasing dose-response relationship evident. In fact, the high exposure level often had a smaller (although nonsignificant) proportion of abnormalities than the low and medium levels.

Interactions were present for 5 of the 10 variables, and occurred primarily in the enlisted groundcrew stratum. A summary of these interactions is presented in Table 11-13.

Meaningful interpretation of the interactions was difficult, due to the small numbers of abnormalities within a covariate strata. No significant adverse effects to participants with higher exposure levels were evident, however, in this analysis.

In summary, no evidence of an increasing dose-response relationship at the followup examination was observed. No increase in prevalence rates was seen as exposure levels increased. These results essentially were in agreement with the findings of the Baseline Study.

TABLE 11-12.

Adjusted Exposure Index Analyses for Neurological Variables by Occupation

Variable	Occupation	Exposure Index: Low Total	Exposure Index: Medium Total	Exposure Index: High Total	Contrast	Adj. Relative Risk (95% C.I.)	p-Value
Neck Range of Motion	Officer	125	127	120	Overall		0.906
					M vs. L	0.82 (0.31,2.18)	0.686
					H vs. L	0.97 (0.37,2.56)	0.955
	Enlisted Flyer	51	61	53	Overall		0.940
					M vs. L	0.79 (0.20,3.20)	0.744
					H vs. L	0.83 (0.21,3.31)	0.786
	Enlisted Groundcrew	148	160	132	Overall		0.299
					M vs. L	0.93 (0.27,3.21)	0.908
					H vs. L	0.36 (0.09,1.51)	0.163
Cranial Nerve Function Index	Officer	120	127	119	Overall		0.551
					M vs. L	0.63 (0.28,1.44)	0.277
					H vs. L	0.78 (0.35,1.78)	0.560
	Enlisted Flyer	51	60	53	Overall		0.808
					M vs. L	1.00 (0.29,3.43)	0.999
					H vs. L	0.68 (0.18,2.59)	0.569
	Enlisted Groundcrew	145	158	131	Overall		****(1)
					M vs. L	****(1)	****(1)
					H vs. L	****(1)	****(1)

TABLE 11-12. (continued)

Adjusted Exposure Index Analyses for Neurological Variables by Occupation

Variable	Occupation	Exposure Index: Low Total	Exposure Index: Medium Total	Exposure Index: High Total	Contrast	Adj. Relative Risk (95% C.I.)	p-Value
Cranial Nerve Function (Neck Range of Motion Excluded)	Officer	120	127	119	Overall		0.148
					M vs. L	0.30 (0.08,1.22)	0.093
					H vs. L	0.36 (0.09,1.45)	0.150
	Enlisted Flyer	51	60	53	Overall		0.860
					M vs. L	1.04 (0.13,8.27)	0.969
					H vs. L	0.56 (0.05,6.58)	0.642
	Enlisted Groundcrew	145	158	131	Overall		0.894
					M vs. L	0.75 (0.23,2.45)	0.639
					H vs. L	0.84 (0.25,2.76)	0.773
Pin Prick	Officer	124	124	119	Overall		0.277
					M vs. L	0.43 (0.13,1.38)	0.156
					H vs. L	0.49 (0.17,1.43)	0.191
	Enlisted Flyer	51	60	53	Overall		0.399
					M vs. L	0.33 (0.05,2.35)	0.267
					H vs. L	1.02 (0.23,4.60)	0.979
	Enlisted Groundcrew	146	159	128	Overall		0.108
					M vs. L	0.86 (0.32,2.34)	0.765
					H vs. L	0.28 (0.07,1.07)	0.062

TABLE 11-12. (continued)

Adjusted Exposure Index Analyses for Neurological Variables by Occupation

Variable	Occupation	Exposure Index: Low Total	Medium Total	High Total	Contrast	Adj. Relative Risk (95% C.I.)	p-Value
Light Touch	Officer	124	124	119	Overall		0.047
					M vs. L	0.39 (0.11,1.40)	0.148
					H vs. L	0.20 (0.05,0.83)	0.027
	Enlisted Flyer	51	60	53	Overall		****(2)
					M vs. L	****(2)	****(2)
					H vs. L	****(2)	****(2)
	Enlisted Groundcrew	146	159	128	Overall		0.777
					M vs. L	1.27 (0.34,4.80)	0.725
					H vs. L	0.74 (0.16,3.35)	0.699
Muscle Status	Officer	125	127	120	Overall		0.105
					M vs. L	0.15 (0.02,1.01)	0.051
					H vs. L	0.57 (0.14,2.30)	0.433
	Enlisted Flyer	51	61	53	Overall		0.979
					M vs. L	0.90 (0.04,22.10)	0.946
					H vs. L	0.74 (0.04,14.77)	0.841
	Enlisted Groundcrew	148	160	132	Overall		****(3)
					M vs. L	****(3)	****(3)
					H vs. L	****(3)	****(3)

TABLE 11-12. (continued)

Adjusted Exposure Index Analyses for Neurological Variables by Occupation

Variable	Occupation	Exposure Index: Low Total	Exposure Index: Medium Total	Exposure Index: High Total	Contrast	Adj. Relative Risk (95% C.I.)	p-Value
Achilles Reflex	Officer	122	126	120	Overall		0.384
					M vs. L	0.43 (0.13,1.46)	0.175
					H vs. L	0.65 (0.21,1.99)	0.448
	Enlisted Flyer	51	60	53	Overall		0.021
					M vs. L	--	--
					H vs. L	0.65 (0.16,2.76)	0.564
	Enlisted Groundcrew	147	160	132	Overall		****(3)
					M vs. L	****(3)	****(3)
					H vs. L	****(3)	****(3)
Tremor	Officer	125	127	120	Overall		0.219
					M vs. L	0.19 (0.02,1.66)	0.132
					H vs. L	0.63 (0.14,2.89)	0.548
	Enlisted Flyer	51	61	53	Overall		0.625
					M vs. L	2.11 (0.19,23.39)	0.542
					H vs. L	2.95 (0.29,30.43)	0.364
	Enlisted Groundcrew	148	160	132	Overall		0.396
					M vs. L	0.91 (0.22,3.66)	0.889
					H vs. L	0.28 (0.03,2.44)	0.248

TABLE 11-12. (continued)

Adjusted Exposure Index Analyses for Neurological Variables by Occupation

Variable	Occupation	Exposure Index: Low Total	Exposure Index: Medium Total	Exposure Index: High Total	Contrast	Adj. Relative Risk (95% C.I.)	p-Value
Gait	Officer	125	127	120	Overall		0.483
					M vs. L	0.26 (0.02,3.25)	0.298
					H vs. L	0.89 (0.12,6.76)	0.912
	Enlisted Flyer	51	61	53	Overall		0.188
					M vs. L	0.64 (0.07,6.05)	0.693
					H vs. L	--	--
	Enlisted Groundcrew	148	160	132	Overall		0.576
					M vs. L	0.42 (0.07,2.51)	0.343
					H vs. L	0.88 (0.19,3.99)	0.868
CNS Summary Index	Officer	125	127	120	Overall		0.123
					M vs. L	0.22 (0.04,1.10)	0.066
					H vs. L	0.57 (0.15,2.10)	0.399
	Enlisted Flyer	51	60	53	Overall		0.930
					M vs. L	1.21 (0.25,5.92)	0.818
					H vs. L	0.90 (0.17,4.80)	0.899
	Enlisted Groundcrew	148	160	132	Overall		****(2)
					M vs. L	****(2)	****(2)
					H vs. L	****(2)	****(2)

--No abnormal participants present in medium exposure index level for Achilles reflex (or high level for gait) in enlisted flyers.

****(1)Exposure index-by-diabetic class interaction--relative risk and p-value not presented.

****(2)Exposure index-by-insecticide exposure interaction--relative risk, confidence interval, and p-value not presented.

****(3)Exposure index-by-age interaction--relative risk, confidence interval, and p-value not presented.

TABLE 11-13.

Summary of Exposure Index-by-Covariate Interactions for Neurological Variables

Variable	Occupation	Covariate	p-Value
CNF Summary Index	Enlisted Groundcrew	Diabetic Class	0.045
Light Touch	Enlisted Flyer	Insecticide Exposure	0.026
Muscle Status	Enlisted Groundcrew	Age	0.026
Achilles Reflex	Enlisted Groundcrew	Age	0.014
CNS Summary Index	Enlisted Groundcrew	Insecticide Exposure	0.010

LONGITUDINAL ANALYSES

Two variables, the modified Romberg sign and the Babinski reflex, were investigated to assess longitudinal differences between the 1982 Baseline examination and the 1985 followup examination. Both variables were classified as abnormal or normal. As shown in Table 11-14, 2x2 tables were constructed for each group for each variable. This table shows the number of participants who were abnormal at the Baseline examination and abnormal at the followup examination, abnormal at Baseline and normal at the followup, normal at Baseline and abnormal at the followup, and normal at both Baseline and the followup. The odds ratio is the ratio of the number of participants who were normal at Baseline and abnormal at the followup to the number of participants who were abnormal at Baseline and normal at the followup (the "off-diagonal" elements). The p-value was derived from Pearson's chi-square test of the hypothesis that there was comparable change in the two groups over time.

These data showed no longitudinal difference in the change pattern in the Romberg sign in the two groups, but they did show a significant change in the Babinski reflex. In the Baseline examination, the Ranch Hands had a significantly greater proportion of reflex abnormalities than the Comparisons, but the followup examination showed approximately the same percentage of abnormality in both groups (Est. RR: 1.02, 95% C.I.: [0.27,3.80, p=0.999]).

SUMMARY AND CONCLUSIONS

Interval questionnaire data (1982 through 1985) on neurological illnesses, verified by medical records, revealed no significant group differences. These data were added to verified Baseline historical information to assess possible differences in the lifetime experience of neurological disease. Again, there was no significant difference between the Ranch Hand and Comparison groups.

TABLE 11-14.

Longitudinal Analysis of Romberg Sign and Babinski Reflex: A Contrast of Baseline and First Followup Examination Abnormalities

Variable	Group	1982 Baseline Exam	1985 Followup Exam Abnormal	1985 Followup Exam Normal	Odds Ratio (OR)*	p-Value (OR_{RH} vs. OR_c)
Romberg Sign	Ranch Hand	Abnormal	2	188	0	0.38
		Normal	0	777		
	Comparison	Abnormal	0	250	0.004	
		Normal	1	886		
Babinski Reflex	Ranch Hand	Abnormal	1	7	0.43	0.04
		Normal	3	953		
	Comparison	Abnormal	0	1	5.00	
		Normal	5	1,129		

$$\text{*Odds Ratio: } \frac{\text{Number Normal Baseline, Abnormal Followup}}{\text{Number Abnormal Baseline, Normal Followup}}.$$

A detailed neurological examination evaluated neurological integrity in three broad areas: cranial nerve function, peripheral nerve function, and central nervous system (CNS) coordination. The summary analytic results for all measurement variables comprising these three functional areas are presented in Table 11-15.

Assessment of the 12 cranial nerves was based on the measurement of 14 variables. Two summary indices were constructed. Both the unadjusted and adjusted analyses did not disclose any statistically significant group differences, although two variables, speech and tongue position, were of borderline significance, with Ranch Hands faring worse than Comparisons. One of the two cranial nerve summary indices was marginally significant, again with the Ranch Hands at a slight detriment.

The unadjusted and adjusted analyses of peripheral nerve function, as measured by eight variables (four reflexes, three sensory determinations, and muscle mass), did not reveal significant group differences.

CNS coordination was evaluated by four measurements and a constructed summary variable. Hand tremor was found to be of borderline significance, with the Ranch Hands faring slightly worse than the Comparisons. The CNS summary index showed a significant detriment to the Ranch Hands.

The exposure analyses for neurological variables with reasonable counts of abnormalities showed only occasional statistically significant results. No consistent pattern with increasing exposure was evident for any occupational category of the Ranch Hand group.

TABLE 11-15.

Overall Summary Results of Unadjusted and Adjusted Analyses of Neurological Variables

Variable	Unadjusted	Adjusted	Direction of Results**
Questionnaire[a] Physical Examination			
Neurological Disease (Interval)	NS[b]	--	
Neurological Disease (History)	NS	--	
Cranial Nerve Function			
Smell	NS	--	
Visual Fields	NS	--	
Light Reaction	NS	--	
Ocular Movements	NS	--	
Facial Sensation	NS	--	
Corneal Reflex	--[c]	--[c]	
Jaw Clench	NS	--	
Smile	NS	--	
Palpebral Fissures	NS	--	
Balance	NS	--	
Gag Reflex	NS	--	
Speech	NS*	--	RH>C
Tongue Position Relative to Midline	NS*	--	RH>C
Palate and Uvula Movement	NS	--	
Neck Range of Motion	NS	NS	
Cranial Nerve Function Index[d]	NS	NS	
Cranial Nerve Function Index[d] (excluding Neck Range of Motion)	NS*	NS*	RH>C
Peripheral Nerve Function			
Pin Prick	NS	****	
Light Touch	NS	NS	
Muscle Status	NS	NS	
Vibratory Sensation	NS	--	
Patellar Reflex	NS	--	
Achilles Reflex	NS	NS	
Biceps Reflex	NS	--	
Babinski Reflex	NS	--	

TABLE 11-15. (continued)

Overall Summary Results of Unadjusted and Adjusted Analyses of Neurological Variables

Variable	Unadjusted	Adjusted	Direction of Results**
Central Nervous System Coordination			
Tremor	NS*	NS*	RH>C
Coordination	NS	--	
Romberg Sign	NS	--	
Gait	NS	NS	
CNS Summary Index[d]	0.036	0.042	RH>C

**RH>C: More abnormalities in Ranch Hand group than in Comparison group.

[a]Disease categories include: inflammatory diseases, heriditary and degenerative diseases, peripheral disorders, disorders of the eye, disorders of the ear, and other disorders.

NS:Not significant (p>0.10).

[b]No inflammatory diseases noted; borderline significant (p=0.069, RH>C) for other disorders; not significant for remaining categories.

--Analysis not performed because of sparse number of abnormalities.

[c]No abnormalities present.

NS*Borderline significant ($0.05<p\leq0.10$).

[d]Constructed variable.

****Group-by-covariate interaction.

In a longitudinal analysis of the Romberg sign and the Babinski reflex, only the Babinski reflex revealed a significant difference between the Baseline and followup examination, with the Ranch Hands converting from significant adverse findings at Baseline to favorable nonsignificant findings at the followup examination.

Overall, the followup examination findings are quite similar to the Baseline findings. However, several distinct patterns were evident from the analyses: (1) The followup examination detected substantially fewer abnormalities for almost all measurement variables, (2) the decrease in abnormalities was equivalent in both groups, (3) most of the covariate effects were classical, although exceptions were evident, (4) the adjusted analyses were uniformly similar to the unadjusted analyses, (5) the constructed summary variables were generally statistically significant, or of borderline significance (however some indices were created after the data were examined), and (6) although statistical significance at the pre-assigned α -level of 0.05 was not achieved for any of the measurement variables, abnormalities tended to cluster in the Ranch Hand group.

Of the three group-by-covariate interactions in the adjusted analyses, only one, a borderline group-by-insecticide exposure interaction for hand tremor, where Ranch Hands exposed to insecticides had a marginally significant adverse effect, was of probable biologic (and operational) significance.

In conclusion, none of the 27 neurological variables demonstrated a significant group difference, although several showed an aggregation of abnormalities in the Ranch Hand group, which merits continued surveillance. Historical reporting of neurologic disease was equal in both groups. The clinical sensitivity in detecting neurological deficits varied substantially between the Baseline and the followup examinations, but the number of statistically significant variables remained about the same. None of the exposure analyses revealed dose-response patterns in the Ranch Hand occupational categories. The longitudinal analyses disclosed a favorable reversal of significant Babinski reflex abnormalities at Baseline to nonsignificant findings at the followup examination for the Ranch Hands. The similarity in results between unadjusted and adjusted statistical tests is evidence of group equality for the traditionally important neurological covariates of age, alcohol, and diabetes. Of three group-by-covariate interactions in the adjusted analyses, only the Ranch Hand insecticide interaction with hand tremor was biologically plausible.

CHAPTER 11

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